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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,689	11/24/2003	Mario Stevenson	UMY-034RCE	3913
959 7590 12/22/2009 LAHIVE & COCKFIELD, LLP FLOOR 30, SUITE 3000 ONE POST OFFICE SQUARE BOSTON, MA 02109			EXAMINER SCHNIZER, RICHARD A	
			ART UNIT 1635	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/722,689

**Applicant(s)**

STEVENSON ET AL.

**Examiner**

Richard Schnizer

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 27 October 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-6, 9-12, 20, 21, 84-90 and 92-94 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 9-12, 20, 21, 84-90 and 92-94 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 24 November 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Final Drawing Review (PTO-849)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

An amendment was received and entered on 10/27/09.

Claims 7, 8, 13-15, 18, 19, 75-83, and 91 were canceled.

Claims 1-6, 9-12, 20, 21, 84-90, and 92-94 remain pending and are under consideration in this Office Action.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6, 9-11, 20, 21, 84, 86-90 and 92-94 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US 5693535) in view of Tuschl et al (US 7056704).

Draper taught ribozymes targeting various conserved sites in HIV RNA including LTR, nef, and vif. See column 4, lines 1-3 and 10-15; and column 9, lines 57-66. The ribozymes are meant to cleave genomic RNA as well as mRNAs expressed from provirus (see column 4, lines 33-37).

Draper did not teach siRNA.

Tuschl taught siRNAs of 21-24 nucleotides (preferably 21 nucleotides) that are structurally and functionally equivalent to dicer cleavage products of longer dsRNAs.

See column 28, lines 15-17. The siRNAs may contain modified nucleotides (column 3, lines 36-44), and mismatches relative to the target sequence are allowed at the termini of the siRNAs (column 28, lines 25-32), for example it is routine to include terminal TT dinucleotides regardless of the target sequence.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute siRNAs of Tuschl for the ribozymes of Draper when targeting HIV RNA for degradation. One would have been motivated to do so because siRNAs are more potent than ribozymes. Tuschl et al stated that "siRNAs are extraordinarily powerful reagents for mediating gene silencing" and that "siRNAs are effective at concentrations that are several orders of magnitude below the concentrations applied in conventional antisense or ribozyme gene targeting experiments." See column 23, lines 15-20. One would have had a reasonable expectation of success because the target sites of Draper were selected on the basis of their availability for hybridization. See column 10, lines 13-23, and 52-63.

The "expressed from a vector" limitation of claim 84, 86 and 87 does not affect the structure of the siRNA, and so receives it no patentable weight. Similarly, claims 88-90, 92, and 93 are included in this rejection because although they recite structural requirements of a vector (e.g. the vector must encode a plurality of siRNAs), these vector structure requirements are given no patentable weight because the claims are drawn to "a small interfering RNA (siRNA)", and not to a vector. The particulars of the vector are not considered to have any effect on the structure of the claimed siRNA, and so are given no patentable weight.

Claims 12 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Draper et al (US 5693535) and Tuschl et al (US 7056704) as applied to claims -6, 9-11, 20, 21, 84, 86-90 and 92-94 above, and further in view of Svoboda et al (Biochem. Biophys. Res. Comm. 287: 1099-1104, 2001).

The teachings of Draper and Tuschl are summarized above and can be combined to render obvious siRNAs directed to portions of an HIV genome. The references did not explicitly disclose shRNAs.

Svoboda taught that shRNAs, expressed from plasmids, were just as effective as dsRNAs comprising separate strands. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute shRNA for siRNA in the invention of Draper as modified by Tuschl. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). Finally, the substitution of shRNA for siRNA would have yielded predictable

results to one of ordinary skill in the art at the time of the invention, in view of the teachings of Svoboda. Thus the invention as a whole was prima facie obvious.

Note, the statement of the rejection above corrects a typographical error in the previous action that indicated that the rejected claims were 13, 14, and 85, instead of 12, 13, and 85. This was clearly a typographical error in view of the fact that claims 12, 13, and 85 are drawn to shRNAs, as are the teachings of Svoboda.

### ***Response to Arguments***

Applicant's arguments filed 10/27/09 have been fully considered, but are not persuasive.

Applicant reiterates arguments set forth previously, alleging that the ribozyme and siRNA arts are non-analogous, and that MPEP 2143(B) does not support substitution of siRNAs for ribozymes because the results obtained would have been unpredictable.

More specifically, Applicant asserts that one would not have had a reasonable expectation of successfully using siRNAs based on the teachings of Draper with regard to site accessibility because ribozymes are much smaller than RISC, and concludes that one could not have reasonably expected there to be no steric hindrance of RISC. This is unpersuasive because it is merely attorney opinion and is not supported by evidence.

Applicant further asserts that there was no reasonable expectation of success in applying siRNA technology to mediate RNA interference of an incoming HIV RNA genome during an early replication cycle event. Applicants maintain their earlier

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established position in this regard. Moreover, Applicant asserts that one of ordinary skill understood that, in the early stages of infection, the viral genome is condensed by core proteins that would protect it from siRNA attack. The fact that the genome is actually accessible to such attack is asserted to be surprising and unexpected, and to support a finding of non-obviousness. Applicant relies for support on Bitko and Barik (2001) who speculated that respiratory syncytial virus genomic RNA is resistant to RNAi cleavage due to its tight association with nucleocapsid protein. This is unpersuasive because RSV is not related to HIV. RSV is a negative strand, nonsegmented virus, whereas HIV is a lentivirus, a positive strand retrovirus. HIV and RSV do not share the same nucleocapsid proteins or genomic structure. The teachings of Barik provide no evidence that one of ordinary skill would have expected condensed HIV genomic RNA to be resistant to siRNA attack. On the other hand, Sarver et al (Science 247: 1222-1225, 1990) showed that ribozymes directed to HIV gag RNA cleaved "incoming viral RNA" when expressed in cells that were subsequently challenged with HIV-1. See abstract; Fig. 4 on page 247; and paragraph bridging pages 247 and 248, especially page 248, left column, lines 16-21. Based on this evidence, one of ordinary skill in the art would have had reason to believe that HIV genomic RNA was accessible to attack by siRNA.

Applicant argues that Sarver fails to show that ribozymes directed to HIV Gag RNA cleaved incoming viral RNA, as explicitly stated by Sarver at page 1225, left column, lines 16-21. Applicant states that Sarver's measurements were based on RNA isolated at 7 days post infection, and that it is now known that genomic RNA is

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destroyed by the cell long before 7 days, concluding that Sarver's conclusions are in error. This is unpersuasive because Applicant has presented no evidence that the interpretation of Sarver is incorrect.

As previously stated in the Action of 4/27/09, even if one of ordinary skill in the art at the time of the invention would have believed that siRNAs could not successfully attack HIV genomic RNA at an early stage of infection, i.e. while condensed by core proteins, the claims would still be unpatentable over the cited art. The combined references would result in siRNAs that would promote the degradation of HIV mRNAs and genomic RNAs that are transcribed from a provirus, i.e. RNAs that are not condensed by nucleoproteins. This is supported by the evidence of record, i.e. Park (2001) who showed that dsRNAs mediated the degradation of HIV transcripts generated from a DNA template. Applicant has not pointed to any structural feature of these obvious siRNAs that would distinguish them from the claimed siRNAs, i.e. siRNAs that promote the degradation of condensed genomic viral HIV RNA during an early viral replication cycle event. This is because there is no structural distinction. Absent evidence to the contrary, any siRNA directed to a proviral mRNA, or to genomic RNA generated from the provirus, will also act on the condensed viral genome at an early stage. Even if this were a surprising and unexpected feature, it would not render the claims non-obvious because it is an inherent characteristic of each and every one of the siRNAs that can target an mRNA or viral genome that is generated from the provirus. Something that is old does not become patentable upon the discovery of a new property, and there is no requirement that a person of ordinary skill in the art would



have recognized this inherent feature at the time of the invention MPEP 2112(I-II). Even if it was not expected at the time of the invention that the siRNAs produced from the combined references would have acted on condensed genomic HIV RNA, the claimed invention would still have been obvious because the rejection is not predicated on the particular activity of acting on condensed genomic HIV RNA. The rejection was predicated on what was known at the time the cited references were published (see MPEP 2141.02 (V)). Because the siRNAs rendered obvious by the prior art are, absent evidence to the contrary, structurally identical to those which can successfully attack the viral genome at an early stage, and the allegedly unexpected characteristic is an inherent feature that was not relied upon in any way to formulate the rejection, the invention as a whole was *prima facie* obvious.

In response to this position, Applicant argues that the claimed compositions were not known composition, and points out that the Examiner has not cited an anticipatory reference. Applicant asserts that obviousness cannot be predicated on what is unknown. The Office Agrees. However, as discussed above, the obviousness rejection was not predicated on what was unknown. It was well known in the prior art that HIV transcripts such as those for *nef* and *vif* could be degraded by ribozymes (Draper et al, above) and that siRNA represented a superior alternative to ribozymes for degradation of RNA transcripts (Tuschl et al, above). Note also that Park et al (2001, of record) taught that siRNAs could inhibit expression of HIV transcripts. The only difference between Park and the instant claims is that the siRNAs of Park were generated in a cell from a precursor dsRNA, and are therefore not considered to be "isolated". In view of

the teachings of Tuschl above, those of ordinary skill prior to the time of the invention could reliably deliver isolated siRNAs to mammalian cells. Accordingly, there was no reason for one of ordinary skill at the time of the invention to doubt that isolated siRNAs could be used to inhibit expression of HIV transcripts. Thus, siRNAs directed to nef or vif HIV transcripts, with all the structural characteristics of those instantly claimed, were obvious to those of ordinary skill prior to the time of the instant invention. The functions of these siRNAs are inherent in their structures. Therefore the claimed siRNAs were obvious prior to the time of the invention, regardless of any allegedly unexpected properties that were inherent in their structures.

Applicant asserts that "for an inherent characteristic to render a claim obvious, the inherent characteristic must be known to one skilled in the art at the time the invention was made", relying for support on *Kloster Speedsteel AB v. Crucible Inc.* 793 F.2d 1565, 1576 (Fed. Cir. 1986). This is unpersuasive because so long as the rejection is not predicated on an unknown inherent feature, that feature need not be known to those of skill. See MPEP 2112 (I-II and V) and 2141.02(V). In this case, the inherent characteristic was not relied upon to formulate the rejection. The structure of the claimed siRNAs was obvious, and any inherent features flow from the structure.

Finally, Applicant argues that the claimed vif, nef, and LTR-targeting siRNAs address a long felt need in the field of HIV therapy: the ability to "sterilize" the cell from a productive infection. This is unpersuasive because there is no evidence of record that the claimed siRNAs are therapeutically effective, so Applicant has presented no evidence that any long felt therapeutic need has been met. Applicant argues that the

fact that the publication of Applicant's results in the journal *Nature* provides evidence of a long felt need. This is unpersuasive, publication in a journal such as *Nature* is indicative of significant results in a topic of scientific interest, but does not necessarily provide evidence of any particular long-felt need.

For these reasons the rejections are maintained.

### ***Conclusion***

No claim is allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the

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hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Tracy Vivlemore, can be reached at (571) 272-0763. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Richard Schnizer/  
Primary Examiner, Art Unit 1635